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Cost-effectiveness of antiretroviral regimens used in post-exposure prophylaxis program at United States' PEPFAR-APIN clinics in a developing country: a retrospective pharmaco-economic analysis

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Abstract

Introduction: An appropriate economic evaluation of post-exposure prophylaxis (PEP) should consider the effectiveness of different regimens prescribed for patients. Studies have not evaluated the comparative effectiveness of different PEP antiretrovirals (ARVs) based on their costs. Therefore, the aim of the present study was to determine the cost-effectiveness of ARVs regimens used for PEP in Nigerian tertiary hospitals.

Material and methods: This cross-sectional study collated patients' demographic and clinical data from PEP databases of United States' President Emergency Plan for AIDS Relief – AIDS Prevention Initiative in Nigeria hospitals. Costs of ARVs were obtained from donors' price list. Effectiveness was measured as the percentage of human immunodeficiency virus (HIV)-negative patients one-month post-PEP. Average cost-effectiveness ratios (ACERs) were computed as the unit cost of the regimens/HIV infection averted (HIA). Probabilistic sensitivity analysis was conducted using 1,000 iterations using Monte-Carlo simulation.

Results: Out of 575 patients identified, 198 (34.4%) had non-occupational exposure. Of the 14 regimens, tenofovir (TDF) + lamivudine (3TC) + ritonavir-boosted atazanavir (ATV/r) was prescribed for 230 (40.00%) patients. HIV-negative results were documented in 129 (22.4%) of the 185 patients with post-PEP test. Zidovudine (AZT) + 3TC + ATV-r was the most effective (95.5%, $n = 63$ of 66) regimen, while TDF + emtricitabine (FTC) + ritonavir-boosted lopinavir (LPV/r) was the most expensive ($23.66). With an ACER of $8.110/HIV infection prevented (95% CI: $8.052-$8.168), TDF + 3TC + efavirenz (EFV) was the most cost-effective regimen.

Conclusions: AZT + 3TC + LPV/r was the most effective regimen, while TDF + FTC + ATV/r was the most expensive. However, TDF + 3TC + EFV combination was the most cost-effective regimen used in providing PEP service to HIV patients in Nigerian hospitals.

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Key words: antiretroviral regimens, APIN, average cost-effectiveness ratio, cost-effectiveness analysis, Nigeria, PEPAR, post-exposure prophylaxis.

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Introduction

Post-exposure prophylaxis (PEP) is an emergency human immunodeficiency virus (HIV) prophylactic strategy [1], in which antiretroviral agents (ARVs) are administered to previously HIV-negative persons to prevent the transmission of HIV after being potentially exposed to the infection [2]. Post-exposure prophylaxis involves the use of ARVs, and its' efficacy in both occupational and non-occupational exposures to HIV depends largely on adherence and completion of a 28-day therapy [3, 4]. The time to commencement of PEP ARV after exposure to the infection is also the key to efficacy of PEP, as initiating the drug therapy after 72 hours of exposure may lead to failure of the intended protection [5, 6]. In all cases, the use of appropriate ARVs combination in correct frequency is also an essential factor that affects the efficacy of PEP.

The use of decision models has allowed the determination of cost-effectiveness of ARVs in PEP. Studies have assessed the effectiveness of PEP intervention from an economic point of view. A study conducted in France compared cost-effectiveness of PEP programs using surveillance data from 1999 to 2003. The authors used a decision tree model to evaluate the cost-effectiveness of PEP from a societal perspective. The cost-effectiveness ratio was €88,692 per quality adjusted life year (QALY) saved. Findings from this study showed that PEP averted 7.7 cases of HIV among 8,958 patients, who received PEP when compared to no PEP. Findings from the study showed that PEP was not cost-effective based on the international standards of US$50,000 per QALY saved as a benchmark. However, when PEP was evaluated among different populations of patients, the outcome was different. PEP was found to be effective after receptive anal intercourse with just one HIV-infected person in both males and females. It was also cost-effective for injection drug users, who shared needles with HIV-infected persons, healthcare workers (HCW) and who were exposed to materials from an HIV-infected patients. The identified routes of exposure were percutaneous route and for men who have sex with men (MSM) through receptive anal intercourse with their partner, whose HIV status was unknown [7].

Effectiveness of PEP depends on the use of appropriately prescribed ARVs in the right combination. Therefore, the appropriate economic evaluation to assess the cost-effectiveness of PEP should not just consider PEP as a program comparing the presence and absence of intervention. Rather, economic evaluation should consider the effectiveness of different regimens used for patients, since it can also be a measure for recommendation of the regimens. An extensive search of literature showed no positive results for the presence of any study that has compared the effectiveness and cost of many ARV regimens used in PEP management, especially in a low- and middle-income country (LMIC) cohort. As much as the drugs are provided free at the moment, the sustainability is not assured. This is evident from the stock-out issue in some low-level facilities. Thus, it is necessary to document the cost-effectiveness of the regimens to guide local policy-makers.

This study was, thus, conducted to determine the cost-effectiveness of different ARVs used in the prevention of HIV infection in exposed individuals, who were enrolled into PEP programs in a number of Nigerian tertiary hospitals.

Material and methods

Study design

This was a cross-sectional study that utilized information from PEP databases of selected tertiary healthcare facilities in Nigeria.

Study settings

First generation hospitals were selected from different zones of Nigeria for this study. Those selected had electronic databases of HIV/AIDS patients, with the support of the United States President's Emergency Plan for AIDS Relief – AIDS Prevention Initiative in Nigeria (PEPFAR-APIN). The selected hospitals were Ahmadu Bello University Teaching Hospital (ABUTH) Zaria, Jos University Teaching Hospital (JUTH) Jos, University of Maiduguri Teaching Hospital (UMTH) Maiduguri, and University College Hospital (UCH) Ibadan.

Study sample and source of data

Data of patients who had comprehensive socio-demographic information provided in the database from 2009 to 2016, and those who assessed the service from only one of the centers during a regimen were used in this study.

The following variables were abstracted from the database: age, gender, educational level, type of exposure (occupational or non-occupational), ARVs used, and post-PEP HIV infection status. The required data was abstracted from File Maker Pro (FMPro) database of institutions into Microsoft Excel (2016).

Comparators

Antiretroviral combinations used in PEP were compared in this study. HIV treatment guideline specified a number of ARVs that could be combined in the management of PEP. Final choice of different ARVs was based on the prescribers' clinical assessment of patients. All the regimens that were used for patients with evidences of laboratory results for HIV one month after commencing PEP were applied in CEA.

Determination of cost

International prices (in dollars) of all antiretroviral agents (data of 2017) provided to PEP patients obtained from the donors were used as the cost of drugs [8]. This was because Nigerian National Health Insurance Scheme (NHIS) did not attached prices to antiretrovirals in their

price list since they are provided free of charge to patients. Therefore, the donor's perspective was applied in this pharmaco-economic analysis. To ensure uniformity, the same list from the same donor was used for the prices of all ARVs. However, all the given prices were adjusted for inflation to the year of the study (2019).

Measurement of effectiveness

Effectiveness of PEP regimens was measured as the percentage of patients who tested HIV-negative after completing the regimens. Laboratory test applied in this regard was the one that was conducted not later than a week after completing PEP management (i.e., a month after exposure). These results were already provided in patients' files, which were stored electronically at APIN headquarters.

Determination of cost-effectiveness

The unit cost of the regimen per one HIV infection averted (HIA) was computed as the average cost-effectiveness ratios (ACER) of the regimen. Before selecting the exact ACER, a probabilistic sensitivity analysis (PSA) was conducted using 1,000 iterations with Monte-Carlo simulation to account for uncertainties. ACER for each regimen was selected after considering a confidence interval set at 95%. The aim of sensitivity analysis was to ensure that the conclusion reached from the findings of the study was robust enough against variations in variables used in the model.

Ethical consideration

Approvals were obtained from the institutional review boards (IRBs) of PEPFAR and APIN, which manage databases used for the study. Only data of patients who provided consent for the use of their information for research purposes were included in the study. The study procedure followed a strict confidentiality protocol; all data obtained throughout the course of this study that related directly or indirectly to the identification of subjects were concealed from any third party, and were not included in any results reported.

Results

Data of 575 patients were identified for PEP services. Of this number, 273 had their type of exposure indicated in the database. Non-occupational exposure accounted for 198 (72.5%) of the 273 patients. The socio-demographic data of the patients are presented in Table 1.

Fourteen PEP ARV regimens were prescribed for different patients in the hospitals. Tenofovir (TDF) + lamivudine (3TC) + ritonavir-boosted atazanavir (ATV/r) was recommended for 230 (40.0%) patients. All the ARVs combinations used for the patients are shown in Table 2.

Table 1. Socio-demographic characteristics of PEP patients

Characteristics	Frequency	Percentage
Age (years)		
< 18	38	6.6
18-25	142	24.8
26-35	260	45.5
36-45	95	16.6
46-55	28	4.9
≥ 56	9	1.6
Total	572	100.0
Gender		
Female	344	59.8
Male	231	40.2
Total	575	100.0
Level of education		
None	38	6.8
Primary	14	2.5
Secondary	65	11.7
Tertiary	439	79.0
Total	556	100.0
Type of exposure		
Non-occupational	198	72.5
Occupational	75	27.5
Total	273	100.0

Table 2. Prescribed antiretroviral treatment for PEP patients in the hospitals

Regimens	Frequency	Percentage
AZT + 3TC + LPV/r	78	13.6
AZT + 3TC + ATV/r	104	18.1
TDF + 3TC + ATV/r	230	40.0
TDF + 3TC + EFV	55	9.6
TDF + FTC + LPV/r	14	2.4
AZT + 3TC	17	3.0
TDF + 3TC	15	2.6
AZT + 3TC + EFV	5	0.9
TDF + 3TC + LPV/r	40	7.0
TDF + FTC + NVP	2	0.3
AZT + 3TC + NVP	8	1.4
ABC + 3TC + LPV/r	5	0.9
AZT + 3TC + ABC	1	0.2
TDF + 3TC + NVP	1	0.2
Total	575	100.0

AZT – zidovudine, 3TC – lamivudine, LPV/r – ritonavir-boosted lopinavir, ATV/r – ritonavir-boosted atazanavir, TDF – tenofovir, EFV – efavirenz, ABC – abacavir, NVP – nevirapine, FTC – emtricitabine.

Table 3. Effectiveness and costs of ARVs regimens used in PEP

PEP regimens	HIV status after PEP		Total	Unit cost (US$)
	Negative	Positive		
AZT + 3TC + LPV/r				
Frequency	11	5	16	23.51
Percentage	68.8	31.2	100.0	
AZT + 3TC + ATV/r				
Frequency	63	3	66	20.10
Percentage	95.5	4.5	100.0	
TDF + 3TC + ATV/r				
Frequency	16	13	29	19.15
Percentage	55.2	44.8	100.0	
TDF + 3TC + EFV				
Frequency	33	9	42	6.35
Percentage	78.6	21.4	100.0	
TDF + FTC + LPV/r				
Frequency	0	7	7	23.66
Percentage	0.0	100.0	100.0	
TDF + 3TC + LPV/r				
Frequency	2	13	15	22.56
Percentage	13.3	86.7	100.0	
TDF + FTC + NVP				
Frequency	1	1	2	7.45
Percentage	50.0	50.0	100.0	
AZT + 3TC + NVP				
Frequency	3	4	7	6.05
Percentage	42.9	57.1	100.0	
TDF + 3TC + NVP				
Frequency	0	1	1	6.35
Percentage	0.0	100.0	100.0	
Total				
Frequency	129	56	185	
Percentage	69.7	30.3	100.0	

AZT – zidovudine, 3TC – lamivudine, LPV/r – ritonavir-boosted lopinavir, ATV/r – ritonavir-boosted atazanavir, TDF – tenofovir, EFV – efavirenz, ABC – abacavir, NVP – nevirapine, FTC – emtricitabine.

Cost and effectiveness of PEP regimens

Out of the 575 patients who received PEP medications, 390 (67.8%) did not report for the post-PEP HIV test. Of the 185 patients with post-PEP HIV test results, 129 (69.73%) were HIV-negative. Post-PEP status was documented for patients on nine of the 14 different regimens used in the centers. The regimen with the highest effectiveness (proportion of patients with negative HIV status not later than one week after completing PEP) was zidovudine (AZT) + 3TC + ATV/r: 63 (95.5%) of 66 patients. The regimen with the highest unit cost (for one complete 28-day PEP cycle) was TDF + emtricitabine (FTC) + ritonavir-boosted lopinavir (LPV/r) with $23.66. The effectiveness and respective cost of each regimen are demonstrated in Table 3.

Average cost-effectiveness ratios of PEP regimens

With an ACER of $8.110/HIA (95% CI: $8.052-$8.168), TDF + 3TC + efavirenz (EFV) was the most cost-effective regimen used for PEP among the patients in the hospitals. TDF + 3TC + LPV/r was the least cost-effective regimen, with ACER of $170.658/HIA (95% CI: $169.391-$171.925). In Table 4, the ACERs of all PEP regimens are presented.

Discussion

The most expensive regimen used for PEP among HIV patients in the four hospitals was TDF + FTC + LPV/r. In contrast, the regimen with the highest number of patients reporting negative HIV status after completing PEP was AZT + 3TC + ATV/r. However, the most cost-effective regimen used in PEP enrollees in all the study centers was TDF + 3TC + EFV. At the same time, TDF + 3TC + LPV/r was the least cost-effective regimen, with a pack of complete regimen selling for more than the national minimum wage.

The clinical outcome that was of interest in this study was the HIV status of patients after completing a PEP course. The effectiveness of each regimen was determined as the percentage of patients with negative HIV test results after completing PEP on the respective regimen. The most effective regimen of the nine regimens of the patients' results of post-PEP HIV test was AZT + 3TC + ATV/r. Almost all the patients tested negative after completing PEP. TDF + 3TC + EFV had the second-best effectiveness result among the nine regiments. The least effective regimens used for the patients were TDF + FTC + LPV/r and TDF + 3TC + nevirapine (NVP). None of the patients who were on either of the two regimens had a negative result after PEP. However, there were more patients enrolled in the former than the latter. The reduced effectiveness results from the use of TDF + FTC + LPV/r could have been caused by adherence issues related to pill burden of the regimen. Pill burden is often a problem in adherence to HIV management and care because of the extended period of the drugs taken by patients. The possible reason why TDF + 3TC + NVP had a poor clinical outcome was either the sub-optimal dosing of NVP in the regimen or the possible adverse effects that the patients might have experienced from NVP. This is a further evidence that none of NVP-based regimens used among the patients in this study had a higher proportion of patients having negative HIV test results compared with positive HIV test results. The findings of the study showed that the most expensive regimen was TDF + FTC + LPV/r, in which its' cost could probably be determined by the presence of FTC in the regimen. All the regimens for

Table 4. Cost-effectiveness ratios of ARVs regimens used in PEP

PEP regimens	Cost-effectiveness ratios (US$/ HIV infection averted)				
	Mean	SD	SEM	95% CI	
				Lower bound	Upper bound
AZT + 3TC + LPV/r	34.437	3.927	0.124	34.194	34.681
AZT + 3TC + ATV/r	21.172	2.516	0.080	21.016	21.326
TDF + 3TC + ATV/r	35.103	3.923	0.124	35.860	35.346
TDF + 3TC + EFV	8.110	0.936	0.030	8.052	8.168
TDF + FTC + LPV/r	Indeterminate				
TDF + 3TC + LPV/r	170.658	20.443	0.646	169.391	171.925
TDF + FTC + NVP	15.023	1.795	0.057	14.911	15.134
AZT + 3TC + NVP	14.200	1.649	0.052	14.097	14.302
TDF + 3TC + NVP	Indeterminate				

AZT – zidovudine, 3TC – lamivudine, LPV/r – ritonavir-boosted lopinavir, ATV/r – ritonavir-boosted atazanavir, TDF – tenofovir, EFV – efavirenz, ABC – abacavir, NVP – nevirapine, FTC – emtricitabine.

treatment and care of HIV that contained FTC in Nigeria were withdrawn after a few months, with the most predominant reason being the cost [9, 10]. Interestingly, three NVP-based regimens were the least expensive ARVs used by PEP patients, with AZT + 3TC + NVP being the cheapest regimen. When both cost and effectiveness were considered in determining the regimen of choice, TDF + 3TC + EFV, the most preferred three-drug regimen for PEP, according to the WHO and Federal Government of Nigeria guidelines, was the most cost-effective regimen. Its' ACER was less than twice the ACER of the second-best regimen in terms of cost-effectiveness. TDF + 3TC + LPV/r, though approved for use in PEP, was the least cost-effective regimen. ACER values of TDF + FTC + LPV/r and TDF + 3TC + NVP were indeterminate because none of them had a denominator (HIV infection prevented).

There is a novelty in the cost-effectiveness assessment conducted in this study. No studies have been reported in the literature evaluating ACER comparing with many ARV regimens used in PEP. Instead, most of the studies assessed the cost-effectiveness of PEP program as a whole. Of all the studies on the effectiveness of PEP, none originated from Nigeria. In a study by Pinkerton *et al.* evaluating cost-effectiveness of PEP services among a cohort of 10,000 patients, the CER of PEP was US$70,000 per infection averted. A cost-utility ratio of US$6,316 was also reported in the study per QALY saved [11]. They went further to compare the outcome for two-drug regimens and three-drug regimens, and reported that an additional agent would have to be added to a two-drug regimen to make three-drug regimen 9% more cost-effective. However, the authors recommended that it would be economically wise to restrict the use of PEP to partners of infected persons as a priority before patients, whose exposure was due to unprotected receptive anal intercourse. They believed that providing PEP treatment to all those who request the service would not be economically efficient. Their study, however, restricted their area of interest to PEP patients following sexual exposure to possible HIV infection. In another study, Pinkerton *et al.* evaluated the outcomes of cost-effectiveness analysis of PEP service for both sexual and injection-drug exposures to HIV, and concluded that the use of standard treatment guideline for PEP was cost-effective compared with not taking any medication [12]. Their findings showed that PEP prevented an average of 1.26 HIV infections, and was able to save health utility of 11.74 QALYs. The program, according to their study, was cost-saving for those patients with partners already HIV-positive. In Herida *et al.* study in France evaluating cost-effectiveness of PEP, QALY was utilized to identify CER of PEP. Their study was robust and involved both occupational and non-occupational exposures to HIV. With a population of about 9,000 patients, they reported that PEP prevented 7.7 HIV infections by saving 64.5 QALY. The CER per QALY saved was found to be €88,692 [7].

All the findings of the above-mentioned studies reported higher CER per HIV infection prevented than the ones that were reported in the current study. The difference is acknowledged from the fact that the other studies estimated the CER of PEP in its' entirety. In contrast, the present study estimated CER based on different regimens that were used in the hospitals; all other studies used PEP as a program for their cost-effectiveness studies.

This study has certain limitations. The use of prevention of HIV after PEP as the sole measure of effectiveness is a limitation. This is based on the realization that the clinical outcome of therapy can include the absence of adverse or side effects. Furthermore, the prices used in the CEA study were drawn from the international price list. One implication of doing that is the non-inclusion of the cost of transportation and duty fees, which could add to the costs of the drugs in Nigeria. International prices of the medications were applied because the Nigerian NHIS price list does not include a cost for ARVs, as they are provided free of charge to patients. Since the same list was used for all the regimens, there

is no bias in the comparison of different regimens used in PEP. It should be noted that the use of ACER in economic evaluation is limited by the absence of a 'true' comparison between the competitors. It, however, comes useful in economic evaluations where there are more than two competitors, as in the present study. Some patients did not return for the post-treatment test, but this would not be considered to have affected the study because they were minority, and they have received the same regimens as other patients.

Conclusions

The current study concludes that the most effective PEP regimen measured as the proportion of patients with negative HIV status after PEP was zidovudine + lamivudine + ritonavir-boosted lopinavir. However, tenofovir + lamivudine + efavirenz combination was the most cost-effective PEP regimen in all the patients that were provided the service. The findings of this study will find use among regulators, policy-makers, and funders on the selection of ARVs combination for PEP program, especially in countries, such as Nigeria that do not contribute most of funds for their HIV programs. Researchers will find the results of this study to be a unique contribution to cost-effectiveness analysis evaluation for being the very first CEA of different PEP regimens, unlike previous studies that only determined CEA of PEP program as a single service.

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Conflict of interest

The authors declare no conflict of interest.

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